Polish Society of Clinical Oncology and Polish Urological Association Guidelines for the diagnosis and treatment of renal cell cancer

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1. Evidence-based guidelines for the management

1.1. Introduction

For all diseases, diagnosis and treatment should follow evidence-based guidelines for management [1]. Prospective clinical trials are the most important source of scientific evidence. Management according to the guidelines is more effective and safe for patients, allows to compare the results obtained in various centers and assess the quality of diagnostic and therapeutic procedures, as well as it is important in terms of didactics.

1.2. Principles of creating guidelines for management

The results of properly designed and conducted clinical trials represent the most important element of guidelines development. The evaluation of research results should be comprehensive and take into consideration a variety of priority conditions. The results of phase III clinical trials with similar assumptions or their meta-analyses are of the greatest value. In special epidemiological justified situations (low cancer incidence rate), the results of non-randomized prospective studies or eventually observations from retrospective comparative studies and case reports may be valuable.

The analyzed prospective studies should use appropriate methods in control groups, it is also advisable to adopt clinically relevant main objectives of the research. Subgroup analyzes should be pre-planned (retrospective analyzes are less valuable). It is important to use adequate assumptions for statistical analyzes. The efficacy and safety of the assessed intervention should be equally evaluated (including the frequency and severity of adverse events [AEs] and toxicity-related treatment discontinuation rate). Determination of the impact on patients' quality of life (QoL) is specifically related to safety and particularly plays a role in palliative management.

An example of a comprehensive evaluation is launched by the European Society of Medical Oncology (ESMO) the ESMO — Magnitude of Clinical Benefit Scale (ESMO-MCBS) [2]. ESMO-MCBS classifies the value and clinical benefits of anti-cancer therapies based on the effect on survival rates, objective response rates, frequency of AEs and quality of life, and relates these parameters to the results obtained with standard treatment. However, radical and palliative treatment methods should be classified separately. The assessment of these parameters allows to determine the magnitude of clinical benefit and is the basis for reimbursement decisions-making. The algorithm for assessing the value of anticancer drugs was also developed by the Polish Society of Clinical Oncology (PTOK) and the Polish Society of Oncology (PTO) [3].

1.3. Level of evidence and strength of recommendation

International scientific societies (e.g. the American Society of Clinical Oncology — ASCO or the National Comprehensive Cancer Network — NCCN in the United States) and institutions evaluating new medical technologies (e.g. the National Institute for Health and Care Excellence — NICE in the United Kingdom) incorporates different methods to classify the quality of the evidence and the strength of recommendation used for the development of guidelines that apply to most patients. All classifications indicate, however, that when establishing guidelines, it is important to be aware of the occurrence of situations requiring an individual approach, taking into account all medical and socio-economic conditions. An example of individualization in the guideline development process is establishing the rules of management for patients with advanced age or concurrent, non-cancer, serious medical conditions.

The PTOK guidelines for the diagnostic and therapeutic management assume 4 levels of the quality of scientific evidence (I, II, III and IV) and 3 categories of recommendations for clinical practice (A, B and C). The aforementioned levels of the quality of evidence and categories of recommendations (detailed in Table 1) are used in the studies of PTOK devoted to particular neoplasms and methods of diagnostic and therapeutic management. Epidemiological conditions and the evolution of the possibilities of diagnosing and treating disease in oncology justify the use of reliable scientific evidence, which is the basis for guidelines development. The guidelines provide the basis for increasing the availability of medically and economically sound management.

Table 1. Evidence quality levels and recommendation categories according to the Polish Society of Clinical Oncology

Evidence quality levels	Recommendation categories
I — evidence from well-designed and conducted randomized controlled trials (RCTs) or meta-analysis of RCTs	A — indications clearly confirmed and absolutely useful in clinical practice
II — evidence from well-designed and conducted prospective observational studies	B — indications likely and potentially useful in clinical practice
III — evidence from retrospective observational or case-control studies	C — indications determined individually
IV — evidence from clinical practice and/or expert opinion	

Table 2. The most important hereditary syndromes associated with renal cell cancer

Syndrome	Gen	Morphological features
Von Hippel-Lindau syndrome	*VHL*	Clear cell carcinoma
Hereditary papillary renal carcinoma (HPRC)	*MET*	Papillary carcinoma, type 1
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	*FH*	Papillary carcinoma, type 2
Birt-Hogg-Dubé syndrome	*FLCN*	Chromophobe carcinoma or oncocytoma
Tuberous sclerosis	*TSC1/2*	Clear cell, papillary, or chromophobe carcinoma
Cowden syndrome	*PTEN*	Clear cell, papillary, or chromophobe carcinoma
Hereditary pheochromocytoma syndrome (PCC)	*SDH B/C/D*	Clear cell carcinoma
Clear renal cell carcinoma associated with chromosome 3 translocations		Clear cell carcinoma

2. Epidemiology

Kidney cancer accounts for 5% of malignant neoplasms in men and 3% in women, and this statistic includes neoplasms originating from the renal cortex and some neoplasms originating from the urinary tract epithelium. Classic renal cell cancer (RCC), originating from the renal cortex, accounts for 80% of all kidney cancer. The highest incidence of RCC is reported in Western Europe and the United States. Overall, in the last 2 decades, there has been a 2% increase in the incidence of RCC annually in both worldwide and Europe. The male gender dominates (the male: female incidence ratio is 1.5: 1), and incidence peaks around age 60–70. according to the National Cancer Registry, in recent years in Poland, there are about 5,000 cases of RCC annually (men — about 3,000, women — about 2,000 cases), and about 2,500 patients die from kidney cancer each year (1,500 and 1,000 patients, respectively).

3. Etiopathogenesis

Kidney cancer occurs most frequently sporadically, and only 2–3% of cases are associated with some family conditions. The exact etiology of sporadic RCC has not been established, however, a higher incidence of RCC has been associated with nicotinism, obesity, and hypertension. In turn, consumption of coffee containing caffeine reduces the risk of RCC, and decaffeinated coffee increases the risk of developing clear cell RCC [4]. Renal cell carcinoma is also more common in patients with chronic kidney disease, dialyzed, undergoing kidney transplantation or in patients with tuberous sclerosis complex (TSC).

Genetic factors associated with an increased risk of developing RCC are primarily inactivating mutations of the von Hippel-Lindau (*VHL*) gene, determining the development of clear cell RCC. Autosomal dominant inherited von Hippel-Lindau disease with germline *VHL* mutations is associated with RCC, central nervous system (CNS) hemangiomas, adrenal medulla tumors and retinal hemangiomas. In turn, mutations in the *BHD* gene are associated with the occurrence of chromophobe RCC (CRCC) and eosinophilic adenoma (oncocytoma), and the *MET* and *FH* genes mutations — papillary carcinomas, type 1 and 2, respectively. The list of the most important hereditary syndromes associated with the occurrence of renal cell cancers is presented in Table 2.

4. Pathology

RCC subtypes arise from different parts of the nephron: proximal tubule — papillary carcinoma and clear cell carcinoma, distal tubule — oncocytoma and chromophobe tumor, collecting ducts of Bellini

— collecting duct carcinoma, renal medulla — renal medullary carcinoma (RMC). Clear cell RCC (ccRCC) accounts for 80% of kidney malignancies in adults, and the remaining 20% comprises a number of histological subtypes characterized by distinct different molecular, histological and cytogenetic features. Papillary and chromophobe carcinomas consist of 80% of non-clear cell carcinomas.

Clear cell renal cell carcinoma (ccRCC) — characterized by the presence of cells with abundant, bright cytoplasm, resulting from fats and glycogen deposits. A characteristic feature of ccRCC is the inactivation of the *VHL* gene, which is detected in 90% of tumors.

Papillary renal cell carcinoma — is the second most common histological subtype of RCC and in 10% of cases is bilateral. In microscopic evaluation papillary or tubulo-papillary structures, foci of calcification and necrosis are visible. Type 2 tumors are more aggressive (Fuhrman grade 2/3) and diagnosed at a higher stage.

Chromophobe renal cell carcinoma — cancer cells often with double nuclei surrounded by a characteristic halo. This tumor metastasizes relatively rarely, even when it is detected at significantly high stage (except the cases of sarcomatous transformation).

Collecting duct renal cell carcinoma — characteristic features include tubulo-papillary structure, a fibrotic stroma and mucinous content. This is highly aggressive neoplasm malignant, with often synchronous metastases at diagnosis. In 22% of cases, characteristic lymphocyte-rich infiltrates are observed.

Renal medullary carcinoma — is rare cancer that occurs most frequently in young black men with hemoglobinopathies and is more common in the right kidney for unknown reasons. It is associated with a very poor prognosis. Cancer cells are poorly differentiated, with eosinophilic cytoplasm. To date, less than 200 cases of renal medullary carcinoma have been described.

Microphthalmia-associated transcription factor (MiT) family translocational renal cell carcinoma — is characterized by the presence of translocations of genes encoding TFE3 and TFEB transcription factors, located on Xp11 and 6p11 chromosomes. This subtype is found in young people, more often in women. Tumors with translocation are very aggressive and associated with early lymph nodes involvement. Macroscopically, tumors are similar to clear cell carcinoma, with cells with very abundant, bright, granular cytoplasm, forming papillary systems or nests. However, these neoplasms are much less responsive to treatment compared to ccRCC.

Eosinophilic adenoma (oncocytoma) —is a benign tumor, accounting for 25% of small (< 3 cm) kidney tumors. In imaging diagnostics it is difficult to differentiate from renal cell carcinoma, and in the microscopic evaluation of biopsy material — from chromophobe carcinoma. Until recently, it was believed that due to the possible coexistence of RCC, the diagnosis of oncocytoma based on biopsy sample evaluation was not sufficient to exclude the malignant lesion. Recent studies have shown that the majority of complex (hybrid) tumors are associated with congenital genetic syndromes. Only less than 5% of sporadic monofocal oncocytomas have complex histologic structure.

According to the International Society of Urological Pathology (ISUP), WHO (2016) and the Polish Society of Pathologists recommendations, histopathological diagnostics of kidney tumors should include:

— tumor histological type;
— the degree of differentiation according to the Fuhrman grading system with ISUP modification (G1–4);
— presence of sarcomatous transformation (always G4 according to ISUP);
presence of necrosis;
— presence of vascular invasion;
— pathological stage according to pTNM (pathological tumor, node, metastasis) classification;
— surgical margin;
— description of non-neoplastic kidney tissue.

5. Diagnostics

Currently, the historical Virchow's triad, including hematuria, back pain in the lumbar region, and the presence of a tumor palpable through the abdominal wall, is rarely found in clinical practice. If present, the Virchow's triad indicates advanced or aggressive disease. In 30% of patients, atypical symptoms may be a consequence of the paraneoplastic syndrome. Now, most renal cancers are detected accidentally in imaging studies performed for other reasons. In the case of clearly suspicious results of imaging examinations (computed tomography — CT or magnetic resonance imagination — MRI), a biopsy prior to surgery is not necessary, but this examination should be performed when surgery is abandoned and systemic treatment is planned. Considering the fact that in approximately 25% of patients renal cancer will be diagnosed with distant metastasis, systematic staging is necessary already at diagnosis. This is particularly important due to the increasingly strong conditions for metastasectomy and the emerging controversy regarding the benefits of nephrectomy in patients with metastatic RCC. Described recommendations are summarized in Table 3.

5.1. Imaging diagnostics

5.1.1. Computed tomography

Computed tomography is the most important method of imaging diagnostics in RCC patients. A typical CT finding in this tumor type is contrast enhancement

Table 3. Diagnostic tests in renal cell cancer

Baseline tests in renal cell cancer
— Abdomen ± pelvis and chest CT
— General blood tests
— Urinalysis
Additional tests in specific clinical situations
— Abdomen ± pelvis MRI
• Contraindications for contrast-enhanced CT
• The need to exclude venous vessels infiltration
— Contrast-enhanced ultrasound (CEUS)
• Evaluation of a small or unclear lesion in the kidney
• Assessment of tumor thrombus extension
— Urine cytology, ureteroscopy, biopsy
• suspicion of pelvicalyceal system tumor
— MRI of central nervous system (CNDS)
• Clinical suspicion of CNS dissemination
— Bone imaging (scintigraphy or in some cases PET-CT)
• Clinical suspicion of bone dissemination
— Biopsy (preferably core needle)
• Primary tumor — when a nephrectomy is not planned
• Metastatic lesions — in case of diagnostic doubts
— Kidney scintigraphy
• Decreased GFR for elective nephrectomy or
• The need for a careful assessment of active renal parenchyma (patient with a single kidney, multifocal disease)
— Genetic tests
• Genetic syndrome suspected.

CT — computed tomography; GFR — glomerular filtration rate; MR — magnetic resonance imagination; PET — positron emission tomography; PET-CT — positron emission tomography-computed tomography; US — ultrasound

[5] — a lesion is considered to show enhancement if the radiodensity difference between pre- and post-contrast images is at least 20 Hounsfield units (HU); increase by 10–20 HU is considered ambiguous and requires further evaluation (MRI, control CT). In small tumors, the contrast enhancement is usually homogeneous, while in large tumors it is heterogeneous due to the presence of necrosis and hemorrhage. Despite the high accuracy in RCC diagnostics, CT may sometimes not be able to reliably distinguish cancer from eosinophilic adenoma (oncocytoma) [6]. In addition, in some cases, RCC shows very small foci of adipose tissue, which could preclude to reliably distinguish cancer from low-fat angiomyolipoma (AML) on CT scan [7]. On the other hand, the presence of minor calcifications/ossifications in the vicinity of adipose tissue foci is characteristic for cancer.

The risk of malignancy in cystic renal lesion visible in CT is stratified according to Bosniak classification [8] (Table 4). It enables the identification of "clearly benign" lesions (categories I, II), "probably benign" lesions requiring further control (IIF), lesions of an indeterminate nature (III) requiring surgery or active surveillance, and typical "clearly malignant" lesions (IV) requiring only surgery.

Both locally recurrent lesions and RCC distant metastases usually show high contrast enhancement on CT scans and progressive enlargement in subsequent examinations. Bone metastases are usually osteolytic — they are visible on CT as foci/areas of bone destruction. In the course of therapy, the nature of metastatic lesions may change from osteolytic to osteosclerotic, with possible enlargement. Such an image, however, may correspond to the focal reconstruction and reactive formation of bone tissue in the course of therapy, and not the progression, which must be taken into account during the radiological evaluation of the CT scan.

In the course of therapy, minor osteosclerotic metastatic lesions may also appear in locations where previously no changes were found. This may be the result of a reactive bone tissue reaction in the topography of previously present metastatic lesions in the bone marrow, which, however, were too small to cause bone destruction visible on CT.

5.1.2. Magnetic resonance imaging

Kidney cancer in T1-weighted MRI images is often isointense (approx. 60%), possibly hypointense. In T2-weighted images, clear cell carcinoma usually shows an increased signal, while papillary carcinoma — a decreased signal, which allows for preliminary determination of the histological subtype already in the imaging examination; in addition, papillary carcinoma is often characterized by the presence of a pseudocapsule. Diffusion weighted imaging (DWI) within neoplastic tissue usually shows diffusion restriction. However, in the case of kidney tumors, DWI has a moderate accuracy in differentiating between malignant and benign lesions [9]. In some cases, MRI can better than CT imaging the involvement of the venous vessels, especially the extent and nature (thrombus/tumor tissue) of the plug in inferior vena cava (IVC) [10]. MRI can also be used instead of CT in case of contraindications to the administration of iodinated contrast agents used in CT and pregnant women [11]. It is estimated that MRI is more accurate than CT in the assessment of cystic kidney lesions in categories IIF and III according to Bosniak, therefore it can be used in case of doubt in the assessment of CT [12]. MRI may also be the preferred imaging method in young patients with concerns about the use of X-rays, especially when multiple control assessments are required [13]. In MRI imaging an intravenous contrast agent containing gadolinium is used, which is contraindicated in the case of significant renal failure due to the risk of developing nephrogenic systemic fibrosis (NSF) [14].

Table 4. The Bosniak classification system of renal cystic masses

Category	Description	Risk of malignancy	Management
I	**A simple, benign cyst with a hairline-thin wall** No visible calcifications, septa or solid elements. No contrast enhancement and homogeneous simple fluid [< 20 Hounsfield units (HU)]	0%	Treatment usually not required. Re-assessment may be considered after 6–12 months to verify the diagnosis.
II	**A benign cyst with thin septum** May contain few hairline-thin septa without measurable contrast enhancement and fine calcification in the wall or septa. This category also includes homogeneous, well-defined, markedly hyperintense cysts ≤ 3 cm in diameter, without contrast enhancement	0–10%	Treatment usually not required. Re-assessment may be considered after 6–12 months to verify the diagnosis.
IIF (*follow up*)	**Cyst not meeting all category II criteria. A well-defined lesion with features requiring further observation** May contain many hairline-thin or minimally thickened septa, with discrete — perceived but not measurable — contrast enhancement, thicker or nodular calcifications of walls or partitions. This category also includes markedly hyperintense intrarenal cysts > 3 cm in diameter, without contrast enhancement	4.7–24%	Extension of diagnostics is necessary Access to previous imaging studies to assess dynamics MRI consideration Thereby, observation every 3–6 months, and every year if a stable image is confirmed
III	**Indeterminate lesions that usually require surgery, but a significant part of them turns out to be mild** With thickened or irregular wall or septa, with measurable contrast enhancement	40–60%	Surgical treatment is usually indicated. In case of contraindications, fine needle biopsy or active surveillance may be considered
IV	**Usually malignant lesions** All category III criteria and a contrast-enhanced soft-tissue component independent of the wall or septa	85–100%	Surgical treatment

5.1.3. Ultrasonography

Ultrasonography (US) is the most frequently used method of imaging diagnostics of the abdominal cavity organs, including the kidneys, therefore it is often the first examination to find focal lesions in the kidneys, including accidentally — without any connection with the underlying disorder being the indication to US examination. In the RCC assessment, ultrasound is characterized by a much lower sensitivity and specificity than CT or MRI: ultrasound detects approx. 85% of kidney cancers > 3 cm in diameter, but only up to 60% of lesions < 2 cm; some of the suspected lesions in ultrasound are verified in CT as pseudotumors [hypertrophic column of Bertin (HCB), dromedary hump). Renal cell carcinoma in approximately 48% of cases is hyperechoic, in 42% of cases isoechogenic, and 10% of cases hypoechoic mass. Small lesions usually show a homogeneous echogram, and the larger ones, similar to on CT, heterogeneous structure related to necrosis and bleeding foci; some of the lesions may show a presence of pseudocapsule.

5.1.4. Radiography

Conventional X-ray examination of bone and chest structures can be used as a method of the initial assessment of metastatic lesions, but then diagnostics should be continued with more advanced techniques (CT).

5.1.5. Bone scintigraphy

Technetium-99m-methyl diphosphonate (99mTc — MDP) scintigraphy is a nuclear medicine technique that has been available for many years and allows for the simultaneous assessment of the entire skeleton, including the search for metastatic lesions. However, in the case of RCC, such lesions are usually osteolytic, which significantly reduces the sensitivity of scintigraphy, indicating the osteoblastic bone reaction to neoplastic tissue [15].

5.1.6. PET-CT

The use of positron emission tomography (PET) combined with computed tomography (PET-CT) in the diagnosis of kidney cancer is quite limited [16]

— compared to other cancers, RCC may not exhibit significant accumulation of the tracer most commonly used in PET — deoxy-glucose labelled with the isotope ^{18}F (FDG), which forces the use of other markers — ^{11}C or ^{18}F-labeled choline or acetate.

Recommendations

— In the detection and staging of RCC, contrast-enhanced multiphase abdominal and thoracic CT should be used (invasion, tumor plug and metastatic lesions) (II, A).
— Due to the slightly higher sensitivity and specificity of MRI compared to CT in neoplastic plugs detection, MRI should be performed to better assess venous involvement, and to reduce total radiation exposure or to avoid administration of an intravenous contrast agent used in CT (II, A).
— Contrast-enhanced ultrasound (CEUS) is highly sensitive and specific in the assessment of kidney abnormalities. Therefore, it can be used to further assess small kidney lesions, neoplastic plug and differentiate of unclear kidney lesions without the need for exposure to ionizing radiation (II, A).
— PET-CT and scintigraphy are characterized by low sensitivity and specificity in the detection and staging of RCC, and therefore should not be routinely used in RCC staging (II, B).

6. Staging and prognostic factors assessment

Clinical stage is the single strongest prognostic factor in renal cell cancer. Five-year survival rates are at the level of 81%, 73%, 53%, and 8% for grades I, II, III and IV according to TNM, respectively [17].

Anatomical cancer staging should consider the risk factors that are not included in the TNM classification. For stages I/II, infiltration of the renal collecting system is a strong negative prognostic factor [hazard ratio (HR) 3.2; 95% confidence interval (CI) 1.4–7.1] [18]. In stage III, the infiltration of the renal collecting system also seems to be a negative prognostic factor (HR 1.49; 95% CI 1.02–2.17) [19]. For stage III, prognostic significance has not been established for the presence of perirenal fat infiltration [20].

Due to the potential benefits of local treatment in oligometastatic disease [21], it is also necessary to perform a detailed staging in patients with stage IV disease. This may allow the selection of a group of patients who may benefit from this local treatment.

The current staging assessment guidelines are included in the 8th Edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM classification 2017 (Table 5).

6.1. Histological subtype

The role of RCC histological subtype as an independent prognostic factor is debatable, especially when taking into account the impact of other variables, however, most analyzes have shown that patients with cancer have a worse prognosis compared to patients with chromophobe and papillary subtypes. Some less frequent subtypes, such as medullary carcinoma, collecting duct carcinoma, and renal cell carcinoma with Xp11.2 translocation, are considered the most aggressive. Additionally, the presence of the sarcomatous component is an independent negative prognostic factor increasing the aggressiveness and risk of tumor dissemination.

The malignancy grade is also an independent prognostic factor, from many years assessed according to Fuhrman scale. The 5-year survival rates for grade 1, 2, and 3/4 were 89%, 65%, and 46%, respectively [22]. The presence of necrosis is an additional unfavorable prognostic factor for clear cell and chromophobe carcinomas [23].

6.2. Molecular biomarkers

Different molecular markers have been assessed in RCC patients, including carbonic anhydrase IX (CAIX), hypoxia-inducible factor 1α (HIF1α), Ki67 proliferation index and 9p chromosome deletion; however, any of them did not affect the accuracy of prognostic models. Currently, none of the described molecular markers are used in clinical practice.

6.3. Clinical factors

The prognostic impact was described for other factors, such as performance status (PS), the presence of cancer symptoms (fever, weight loss), paraneoplastic syndromes, obesity, laboratory abnormalities (anemia, thrombocytosis, hypercalcemia), systemic inflammatory reaction (CRP, C-reactive protein), neutrophil-lymphocyte ratio (NLR). Based on these observations, numerous models and nomograms were developed and validated for the comprehensive analysis of independent prognostic factors in order to assess the risk of recurrence in patients after radical treatment of RCC. However, the use of UISS system (UCLA Integrated Staging System) [TNM, ECOG (Eastern Cooperative Oncology Group) PS, Fuhrman scale], SSIGN (Stage, Size, Grade, and Necrosis Score) or the Karakiewicz nomogram (TNM, tumor symptoms, Fuhrman scale, tumor size) in making therapeutic decisions is limited due to the lack of adjuvant treatment options and the lack of the highest level data on optimal follow-up after treatment.

Table 5. TNM classification of RCC staging according to AJCC/UICC, 8th edition

T — primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidney		
T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidney		
T1b	Tumor > 4 cm but ≤ 7 cm in greatest dimension, limited to the kidney		
T2	Tumor > 7 cm in greatest dimension, limited to the kidney		
T2a	Tumor > 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney		
T2b	Tumor > 10 cm, limited to the kidney		
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia		
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia		
T3b	Tumor grossly extends into the vena cava below the diaphragm		
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)		
N — regional lymph node			
Hilar, abdominal periaortic and vena cava lymph nodes. Category N is not affected by the side with the nodes			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
M — distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
Clinical staging			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
T1, T2, T3	N1	M0	
Stage IV	T4	Any N	M0
Any T	Any N	M1	

6.4. Prognostic factors in metastatic renal cell carcinoma

In the case of stage IV RCC, in which the patient's assignment to one of the prognostic groups is the basis for qualification for systemic treatment, it is currently recommended to use the IMDC (International Metastatic RCC Database Consortium) prognostic model (Table 6), but it should be remembered that in the majority of systemic therapies available in Poland, qualification for treatment is based on the older MSKCC (Memorial Sloan Kettering Cancer Center) criteria. The accuracy of these scales has been validated, but it should be remembered that the MSKCC is based on database dedicated to interferon-alpha (IFN-α) effectiveness, and the IMDC scale is based on data on the use of anti-angiogenic therapies, hence their nature may not keep up with the rapidly changing treatment landscape of generalized kidney cancer.

7. Treatment

7.1. Management of localized RCC

7.1.1. Active surveillance

Elderly patients or patients with comorbidities and a small kidney tumor have a relatively low risk of RCC-related death compared to the risk of death from other causes [27, 28]. Therefore, in such patients, it is advisable to use active surveillance (AS), which consists in monitoring the disease with the use of available imaging

Table 6. The prognostic scales in RCC

MSKCC scale (developed on the basis of studies with IFN-α) [24]		
Risk factors	**Prognostic category**	**Median overall s urvival (months)**
— Karnofsky performance status score < 80%	Favorable: 0 factors	30
— Time from diagnosis to systemic treatment < 1-year	Intermediate: 1–2 factors	14
— Hemoglobin level < LLN	Unfavorable: ≥ 3 factors	5
— Corrected calcium concentration > ULN		
— Lactate dehydrogenase (LDH) concentration > ULN		
IMDC scale (developed on the basis of studies with TKI-VEGFR) [25, 26]		
Risk factors	**Prognostic category**	**Median overall s urvival (months): first-line [25]; second line [26]**
— Karnofsky performance status score < 80%	Favorable: 0 factors	**43.2;** 35.3
— Time from diagnosis to systemic treatment < 1 year	Intermediate: 1–2 factors	**22.5;** 16.6
— Hemoglobin level < LLN	Unfavorable: ≥ 3 factors	**7.8;** 5.4
— Corrected calcium concentration > ULN		
— Neutrophil count > ULN		
— Platelets count > ULN		

LLN — the lower limit of normal; ULN — lower limit of normal

tests (USG, CT or MRI) and possible implementation of oncological treatment in the case of a clearly progressed neoplastic process. The growth rate of kidney tumors is usually slow, and generalization of the disease is rarely observed during AS [29]. In 2015, the results of a prospective, multicenter study on AS in patients with incidentally detected kidney tumors DISSRM (Delayed Intervention and Surveillance for Small Renal Masses) were published [30]. Almost 500 patients with kidney tumors <4 cm participated in the study and were qualified for either surgery or AS. Patients assigned to AS group were usually older and had worse PS, more comorbidities, smaller tumors and more often multifocal or bilateral lesions. The tumor growth dynamics in the AS population was (median) 0.09 cm/year and decreased with the follow-up. None of the patients with AS died, and none developed metastatic disease. The percentage of patients surviving 2 and 5 years was 98% and 92% (surgical treatment) and 96% and 75% (AS), respectively, and there were no statistically significant differences. Moreover, the 5-year cancer-specific survival rates were 99% (surgical treatment) and 100% (AS) [30, 31].

Active surveillance should be distinguished from close monitoring, i.e. management of patients with contraindications to oncological treatment, in whom diagnostic imaging should be carried out only in case of clinical indications.

7.1.2. Ablative methods

One of the treatment modalities for small renal masses (SRM) is a thermal ablation in the form of cryoablation (CA) or radiofrequency ablation (RFA). The evidence regarding the effectiveness of thermal ablation methods in the treatment of SRM come mainly from retrospective studies and systematic reviews.

7.1.2.1. Cryoablation (CA)

Cryoablation can be performed by both percutaneous and laparoscopic methods. The available — mainly retrospective — studies comparing the two techniques do not indicate any advantage of either of them in terms of perioperative as well as oncological outcomes, except for a shorter hospitalization time with the use of percutaneous method [32, 33]. The results of studies comparing nephron sparing surgery (NSS) performed by different techniques (open, laparoscopic or robot-assisted) with CA of kidney tumor (percutaneous or laparoscopic technique) are inconclusive. Some of them show no differences in overall survival (OS), cancer specific survival (CSS), recurrence-free survival (RFS) and disease-free survival (DFS), local recurrence rate of progression to metastatic disease [34, 35], while others demonstrate the advantage of NSS [36, 37]. Importantly, none of the published studies indicates a prognostic advantage of CA over NSS. Studies comparing the perioperative NSS and CA outcomes are also inconclusive. Some of them show shorter hospitalization time and lower blood loss in patients undergoing CA [34, 35], with no differences in other perioperative outcomes, such as recovery time, complication rate, postoperative serum creatinine concentration. Based on the available studies, it is not

possible to assess which of these methods is associated with a lower risk of developing a newly diagnosed chronic kidney disease.

7.1.2.2. Radiofrequency ablation (RFA)

As with CA, RFA can be performed either percutaneously or laparoscopically. Both techniques show no differences in both the complication rate and oncological outcomes [38–40]. One study found a higher percentage of incomplete ablations with percutaneous access than with laparoscopic method [41]. The results of studies comparing RFA and NSS are inconclusive. One study showed comparable OS and CSS for both treatment methods [42]. Another study, on the other hand, suggests improved OS in patients undergoing NSS, but those patients were younger [43]. A systematic review [44] showed a higher local recurrence rate for RFA compared to NSS, with no difference in terms of distant metastases. A 2018 systematic review comparing thermal ablation (RFA or CA) with NSS showed higher total mortality and cancer-specific mortality for ablation methods, with no difference in the risk of metastasis and local recurrence [45]. The RFA and NSS methods show no differences in the complication rates and the postoperative glomerular filtration rate (GFR) [44], while a systematic review comparing ablative techniques (RFA or CA) with NSS showed a lower complication rate and a lower GRF reduction for ablation methods [45]. The available studies comparing RFA and CA [46, 47] show comparable OS, CSS and RFS for both thermal ablation techniques. The local recurrence rates in one of the studies are higher for RFA [47], and in the other for CA [46]. Postoperative complications rates are comparable [46].

Other ablation techniques, such as microwave, ultrasound, and laser ablation, are considered experimental in the treatment of kidney tumors due to the lack of sufficient scientific evidence.

Recommendations

— Thermal ablation is an alternative to partial nephrectomy in elderly and/or burdened with concomitant abnormalities (e.g. impaired renal function) patients with single T1a cortical renal tumors (III, C).
— Prior to treatment, a tumor biopsy should be performed using the thermal ablation method (IV, A).

7.1.3. Nephrectomy

7.1.3.1. Total versus partial nephrectomy

There is little evidence regarding the direct comparison of NSS and radical nephrectomy (RN) with respect to oncological outcomes, and the available evidence comes mainly from retrospective studies. One randomized trial [48] and several retrospective series [49–51] found comparable results for CSS after NSS and RN in patients with small renal masses (pT1). Due to conflicting results, the beneficial effect of NSS on OS compared to RN suggested in some studies remains unconfirmed [52–54]. A Cochrane systematic review found that NSS was associated with a shorter OS compared to RN in renal cancer limited to the kidney, while CSS and time to relapse and serious complication rates were similar [52]. In comparisons of NSS and RN the complication rate, length of hospital stay estimated blood loss, and blood product transfusions were similar [50–52, 55, 56]. A randomized trial showed that in patients with small kidney tumors and a properly functioning second kidney, NSS can be performed safely, with a slightly higher complication rate compared to RN [57]. Partial nephrectomy is associated with better preservation of renal function than RN [55]. Some studies suggest a reduced risk of cardiovascular disease after NSS [55, 58]. The quality of life after NSS is rated higher than after RN [55].

In a systematic review and meta-analysis of studies comparing NSS in relation to RN, cT1b and T2 tumors were less likely to relapse and cancer-specific and total mortality were lower after NSS. For T2 tumors, NSS was associated with greater blood loss, a greater risk of complications, a lower relapse rate, and lower cancer-specific mortality [59]. In a retrospective long-term, follow-up (LTFU) study (median 102 months) assessing survival in patients with renal tumors ≥ 7 cm undergoing NSS or RN, significantly better median OS and CSS were found [60].

7.1.3.2. Laparoscopic versus open nephrectomy

There are no randomized trials comparing the oncological outcomes of laparoscopic and open RN. A cohort study [61] and retrospective studies have shown that laparoscopic nephrectomy is associated with similar oncological outcomes in relation to open nephrectomy [51]. One randomized study and several non-randomized trials have shown that laparoscopic nephrectomy was associated with shorter hospitalization, less need for painkillers, and less blood loss (but with no difference in blood transfusions) compared to open nephrectomy [51, 62]. However, there were no differences in delayed complications or in postoperative quality of life, and the surgery duration was shorter in the case of open nephrectomy. A systematic review reported fewer complications in patients undergoing laparoscopic RN [55]. There were no significant differences between the transperitoneal and retroperitoneal approach [63, 64]. In a systematic review, no significant differences were found in local recurrence rates between laparoscopic and robot-assisted RN [65].

7.1.3.3. Laparoscopic versus open partial nephrectomy

In centers with extensive experience in laparoscopy, there were no differences between open and laparoscopic partial nephrectomy with regard to RFS and OS

[66, 67]. Blood loss was lower with laparoscopic surgery, but there were no differences in postoperative mortality, thrombosis or pulmonary embolism (PE) [67, 68]. The duration of surgery and the duration of warm ischemia are longer with laparoscopy [67, 68]. Retroperitoneal and transperitoneal approach in laparoscopy is associated with similar perioperative outcomes. Simple enucleation is associated with similar progression-free survival (PFS) and CSS compared to standard NSS and RN [69]. A retrospective analysis comparing open, laparoscopic and robot-assisted NSS with a median follow-up of 5 years showed similar rates of local recurrences, distant metastases, and cancer deaths [70]. In a prospective study comparing the perioperative outcomes of open and robot-assisted partial nephrectomy, the latter was associated with less blood loss and shorter hospitalization stay. Other parameters were similar [71]. In the analysis of the results of 1800 open and robot-assisted NSS, a lower percentage of complications and transfusions, as well as, a shorter hospitalization stay were found in the group undergoing robot-assisted NSS [72]. A meta-analysis comparing the perioperative outcomes of robot-assisted and laparoscopic NSS found that conversion to open surgery and RN was less frequently required in the case of robotic surgery, warm ischemia time and hospitalization stay were shorter, and the magnitude of GFR changes after surgery was also smaller. There were no significant differences in complications, duration of surgery, blood loss, changes in serum creatinine levels after surgery, or positive surgical margins. There were no significant differences in complications, duration of surgery, blood loss, changes in serum creatinine levels after surgery, or positive surgical margins [73]. The studies suggest that the number of procedures (NSS in general/robot-assisted NSS) performed in a clinical center (hospital volume) influences outcomes in terms of surgical complications and margins [74, 75].

7.1.3.4. Management of positive surgical margins

Positive surgical margins are found after about 2–8% of NSS [73], and more often in the case of forced indications and the presence of unfavorable pathological features [76, 77].

The influence of positive margins on oncological outcomes has not been clearly defined, however, based on the literature data, it can be concluded that their presence is not associated with a higher recurrence risk [78]. This is most likely due to the thermal destruction of tissues, including neoplastic cells, located in the immediate vicinity of the surgical incision line. Therefore, in the case of positive margins, only closer monitoring is recommended [77, 79].

7.1.3.5. Lymphadenectomy

The indications for lymphadenectomy in patients without clinically suspicious lymph nodes undergoing NSS and RN are under discussion. Clinical evaluation is based on imaging studies and intraoperative palpation. The value of lymphadenectomy in patients with clinically unsuspected lymph nodes (cN0) was assessed primarily in a single randomized trial (EORTC 30881) [80] which showed that nodal metastases are rare (4%) and the benefit of extended lymphadenectomy is limited only to determine the degree of pathological disease stage. In a large retrospective study, lymphadenectomy in high-risk renal cancer patients was not found to be associated with a reduced risk of distant metastasis, cancer-specific and overall mortality [81]. In other studies, lymphadenectomy has been associated with improved disease-specific survival outcomes in patients with pN+ feature or unfavorable prognostic factors [82, 83]. Retrospective studies indicate that extended lymphadenectomy should involve the lymph nodes surrounding the adjacent large vessel and the area between the aorta and inferior vena cava (IVC). At least 15 lymph nodes should be removed [83].

7.1.3.6. Adrenalectomy

In a prospective, non-randomized clinical trial, tumor size was found to be predictive for adrenal involvement, contrary to tumor location in the upper kidney pole. Adrenalectomy has not been found to affect the prognosis of OS [84].

7.1.3.7. Embolization

There is no benefit associated with tumor embolization prior to routine nephrectomy [85, 86]. In patients not eligible for surgery or with unresectable disease, embolization may help control symptoms (e.g. hematuria or pain in the lumbar region) [87].

Recommendations

— Active surveillance should be considered in elderly patients with ECOG performance status ≥ 2, with comorbidities and a small (< 4 cm) lesion in the kidney (II, B).
— Partial nephrectomy should be performed in patients with T1 tumors (III, B).
— Laparoscopic radical nephrectomy should be performed in patients with T2 tumors and tumors limited to the kidney for whom partial nephrectomy cannot be performed (II, B).
— Minimally invasive radical nephrectomy should not be performed in patients with T1 tumors for whom partial nephrectomy is possible (this includes any approach, including open) (II, B).
— Minimally invasive surgery should not be performed if such approach may worsen oncological and functional or perioperative outcomes (III, B).

Table 7. Comparison of the most frequently used classification of kidney cancer extension

The outreach of kidney cancer extension	Pritchett [89]	Wilkinson [90]	Libertino [91]	Neves [92]	Novick [93]	Hinmann [94]
IVC	1	I	1	0	I	1
IVC < 2 cm above RV	1	II	1	II #1		
IVC > 2 cm above RV and below HVs	1	II	1	II	II	1
IVC above HVs and below the diaphragm	2	II	1	III	III	2
IVC above the diaphragm	3	III	2	IV	IV	2 or 3

IVC — inferior vena cava; RV — renal vein; HVs — hepatic veins

— Extended lymphadenectomy should be considered in patients with unfavorable clinical features, including a large diameter of primary tumor (II, C).
— If positive margins are found after partial nephrectomy, it is not recommended to extend the procedure, but only closer monitoring (III, C).
— Adrenalectomy should not be performed on the kidney tumor side if the preoperative imaging studies do not reveal adrenal involvement (III, B).
— In patients not eligible for surgical treatment with massive hematuria or pain in the lumbar region, tumor embolization should be considered (III, C).

7.2. Treatment of RCC with tumor extension

Tumor extension (TE) that grows into the lumen of the venous system is an unfavorable prognostic factor, while the outreach of tumor extension within the renal vein, inferior vena cava and/or cardiac cavities is not proportional to the risk of metastases [88] (Table 7).

Surgery is the treatment of choice in patients with RCC with tumor extension and without metastases, regardless of the outreach (level) of TE [92, 95, 96]. The choice of the surgical technique depends on tumor extension level (Table 8).

In patients with RCC with TE, minimally invasive surgeries are characterized by a shorter recovery time compared to open surgeries (including and/or sternotomy with the use of extracorporeal circulation). No significant differences were observed in the oncological outcomes after surgery with the use of peripheral cardiopulmonary circulation in deep hypothermia and under normothermic conditions with IVC clamping without supporting by extracorporeal circulation [97]. Preoperative embolization of the renal arteries is not justified, as in patients undergoing such procedure, a longer duration of surgery, greater blood loss, longer hospitalization time and higher perioperative mortality have been reported [97].

As in the case of RCC without TE, lymph node involvement or distant metastases in RCC patients with TE in the venous system is an unfavorable prognostic factor. The 5-year cancer-specific survival rate in the case of metastatic lymph nodes is 0–27%, while in patients with N0 feature it is 17–63% [98–100]. The presence of distant metastases in RCC patients, regardless of venous system involvement by TE, is a negative prognostic factor. The 5-year overall survival rate in RCC patients with N0M0 feature, depending on the outreach of tumor extension, is 55% (TE limited to the sub-diaphragmatic inferior vena cava) or 36% (TE above the diaphragm), and 35% in patients with N1 or M1 feature (TE in renal vein), 24% (TE in IVC below the diaphragm) and 23% (TE above the diaphragm).

Recommendations

— In the case of non-metastatic renal cell cancer with neoplastic extension growing into the lumen of the venous system, surgical excision of the kidney and TE is recommended, regardless of its outreach (II, B).
— It is not recommended to embolize renal arteries prior to excision of RCC with TE growing into the venous system, regardless of its outreach (II, C).

7.3. Treatment of inoperable/metastatic RCC

7.3.1. Choosing the optimal strategy

When deciding on the optimal management strategy in patients with advanced RCC, a number of factors related to both the patient's general condition and the features of disease should be taken into account. First, it is necessary to assess the possibility and justifiability of local treatment (primary tumor resection, resection/radiosurgery of metastatic lesions), and only in the next step to consider the systemic treatment strategy (Fig. 1). The decision regarding the introduction of systemic treatment must take into account stage and dynamics of the disease, accompanying symptoms and the possible presence of an immediate threat to the patient's life, related, for example, to the so-called organ crisis. In the case of high disease dynamics, massive advancement or symptoms of an organ crisis, systemic treatment must

Table 8. Types of approaches and surgical technique depending on the outreach of kidney cancer extension (according to the Neves classification [92])

Incision	Technique
Tumor extension level: 0	
Lumbar	IVC control below and above TE
Subcostal	
Middle abdominal	
Possible 3- or 5-port laparoscopy	
Possible robotic surgery	
Tumor extension level: I	
Lumbar (only for tumor of the right kidney)	IVC control below and above TE and RV of the healthy side and performing thrombectomy
Subcostal	
Middle abdominal	
Possible 3- or 5-port laparoscopy	
Possible robotic surgery	
Tumor extension level: II	
Chevron incision	IVC control below and above TE and RV of the healthy side and performing thrombectomy
Chevron incision with a median extension	
Middle abdominal	
Possible laparoscopy	
Possible robotic surgery	
Tumor extension level: III	
Chevron incision with a median extension	IVC control below and above TE, RV of the healthy side and HVs and performing thrombectomy
Middle abdominal	
Thoracoabdominal	
Tumor extension level: IV	
Chevron incision with a median extension	Removal of TE from the right atrium using a Foley catheter, manual fingers technique: "up-down", or lowering of the TE into the sub-diaphragmatic part of IVC
Thoracoabdominal	
Middle abdominal with sternotomy	
Possible laparoscopy with open atriotomy	

TE — tumor extension; IVC — inferior vena cava; RV — renal vein; HVs — hepatic veins. The tumor extension level was classified by [6]

be implemented as soon as possible (even in patients without prior nephrectomy). In the case of patients with oligometastatic disease or multiple, but asymptomatic and potentially slowly growing metastases, especially located in a single site, the first delay in the introduction of systemic treatment and leaving the patient under active surveillance (AS) or referring to local treatment (nephrectomy, metastasectomy, stereotactic radiotherapy of metastatic lesions) should be considered. In such a situation, it is possible to safely postpone systemic treatment for up to several months without its effectiveness adversely affected. The phase II study assessed the safety of AS in previously untreated, asymptomatic patients with metastatic RCC [101]. A group of 52 patients underwent control imaging examinations every 3 months in the first year, every 4 months in the second year, and every 6 months in the following years. The median follow-up was 38.1 months, and the median time from the start of AS to systemic treatment was 14.9 months. The prognostic factors suggesting the advantage of AS include the presence of up to one unfavorable prognosis factor according to the IMDC scale and metastases located in no more than two organ sites. In the group of patients with favorable prognostic factors, the median AS time was 22 months, while in patients with unfavorable factors — 8.4 months [101]. In any other case, adequate systemic treatment should be implemented (Fig. 2).

7.3.2. Cytoreductive nephrectomy

The role of cytoreductive nephrectomy (CN) in patients with metastatic RCC is currently the subject under many debates. Historically, nephrectomy in patients with metastatic RCC undergoing IFN-α-based

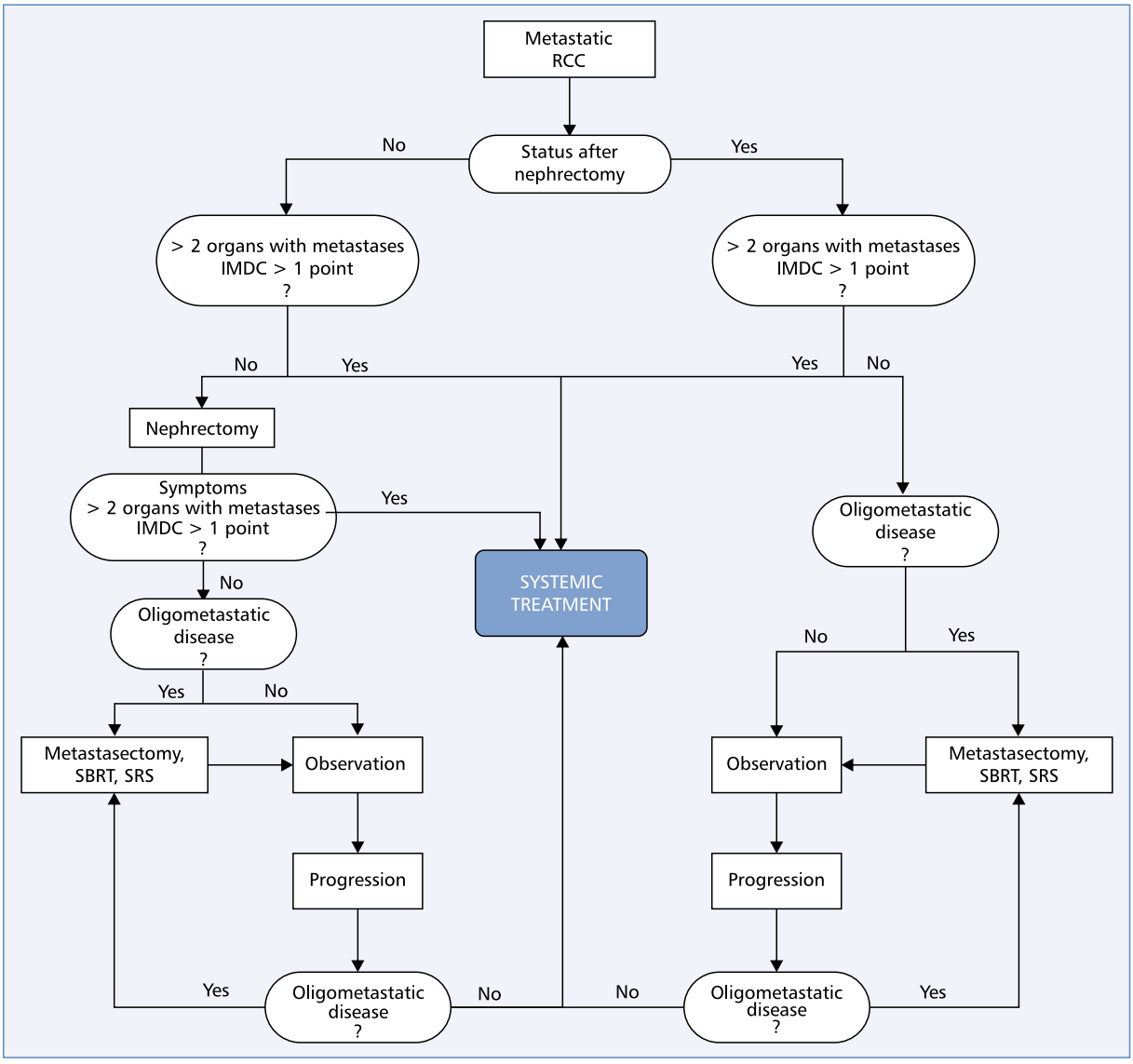

Figure 1. Management strategy in patients with advanced RCC. SBRT — stereotactic body radiation therapy; SRS — stereotactic radiosurgery

immunotherapy has been shown to significantly improve prognosis, reducing the relative risk of death by more than 30% [102]. Due to this fact, primary tumor resection has become a standard procedure in all RCC patients, regardless of disease stage. Thus, at the time of the commencement of studies on targeted therapies in the treatment of RCC, the absolute majority of patients qualified for these studies underwent nephrectomy of radical or cytoreductive intent. Therefore, it was very difficult to conclude about the value of CN in the era of molecularly targeted treatment. Retrospective analysis of the US National Cancer Data Base, covering the years 2006–2013 [15.4 thousand patients treated with tyrosine kinase inhibitors (TKIs), including 35% of patients undergoing CN] showed that CN was associated with a significant reduction of the relative risk of death by 55% (HR 0.45; 95% CI 0.40–0.50) with OS median of 17.1 months (patients after CN) and 7.7 months (patients without CN), respectively [103].

So far, only two prospective clinical trials (CARMENA and SURTIME) with incomplete recruitment have been conducted to assess the role of CN in patients with metastatic RCC receiving sunitinib [104, 105]. The CARMENA study verified whether systemic treatment without preceding CN is non-inferior to systemic treatment after CN. The study included 450 patients (intermediate and poor prognosis according to MSKCC scale) randomly assigned to the experimental arm with CN and sunitinib or to the control arm with sunitinib alone. In the experimental arm, CN was performed

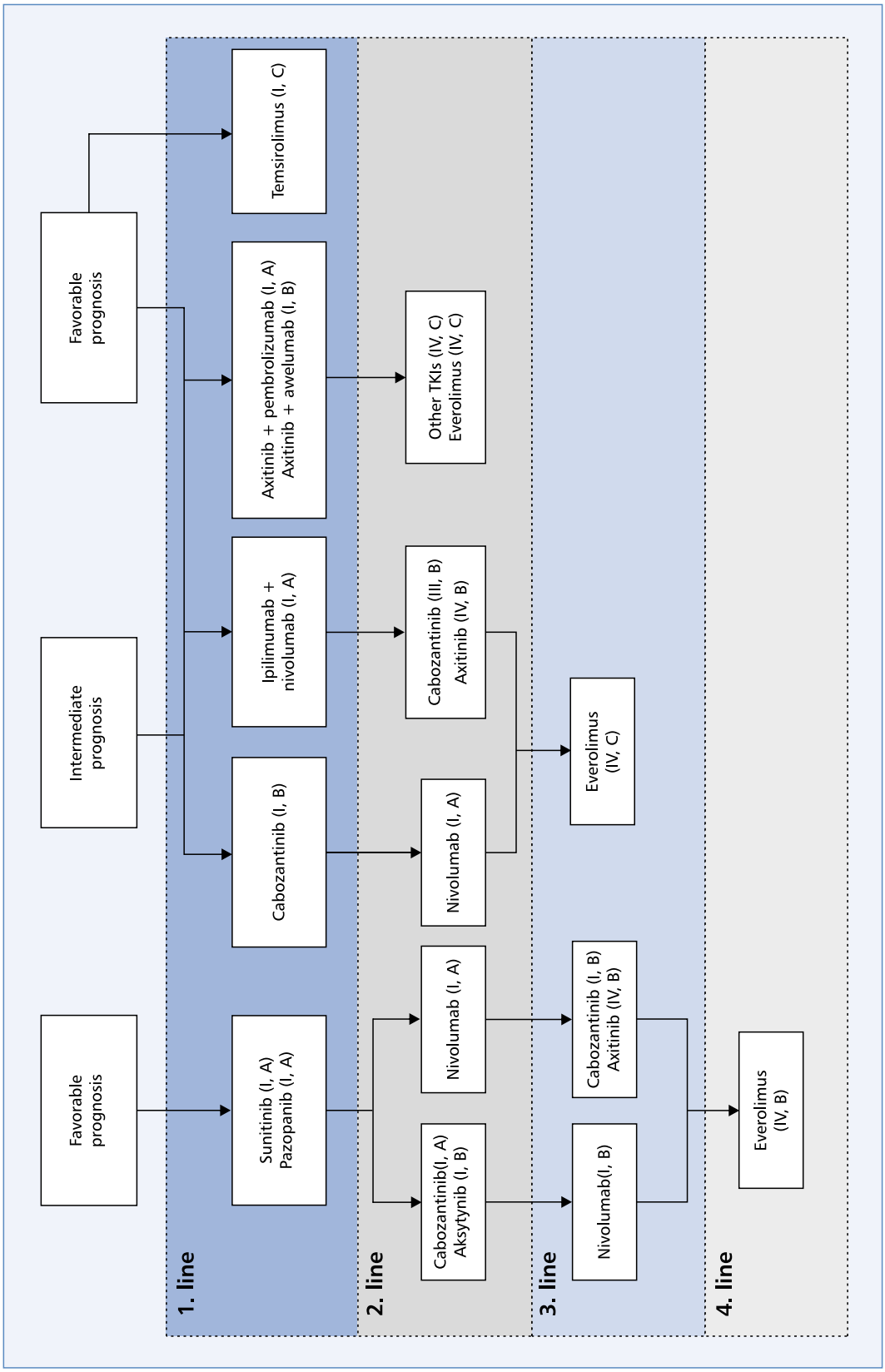

Figure 2. Systemic treatment of advanced ccRCC. TKI — tyrosine kinase inhibitors

within 4 weeks of randomization, and sunitinib was administered within 3-6 weeks after CN. In the control arm, sunitinib was started within 3 weeks of randomization. In the intention-to-treat (ITT) population, the median OS (18.4 months) was not significantly higher in the non-CN arm than in the CN arm (13.9 months), which met the assumed non-inferiority boundary. In turn, the SURTIME study compared the effects of immediate and deferred CN in RCC patients receiving sunitinib on 28-week PFS. In a population of 99 patients participating in this study, no significant differences in relation to the indicated parameter were found, however, a significant reduction in the relative risk of death was demonstrated in patients undergoing delayed CN (HR = 0.57; 95% CI 0.34–0.95) with a median of OS 32.4 months (deferred CN) and 15 months (immediate CN), respectively. Summarizing the results of the CARMENA and SURTIME studies, it can be unequivocally concluded that CN is not necessary in patients with metastatic RCC. However, a detailed analysis of the CARMENA study indicates that the adverse effect of CN on prognosis is particularly evident in the group of patients with ≥ 2 factors of poor prognosis according to IMDC scale [106]. In clinical practice, this means that taking into account the beneficial impact of CN on the immune system functions, manifested by spontaneous remissions or long-term disease stabilization [107, 108], CN is a valuable option in patients with good performance status and tumor-related symptoms or patients without massive dissemination and metastases-related symptoms.

7.3.3. Metastasectomy

Surgical treatment or radiosurgery/stereotaxic radiotherapy of metastatic lesions is an increasingly used procedure in the oncological treatment of patients with oligometastatic neoplastic disease. The basic assumption of such a procedure is to reduce the overall tumor mass, which should translate into improved prognosis. Additionally, in many cases, local treatment may delay the implementation or change of systemic treatment strategy. First mentions of a metastasectomy (MX) in RCC patients appeared over 80 years ago [109]. Although no randomized clinical trials have been conducted so far, it is assumed based on numerous observational studies that such a procedure may improve the prognosis. A systematic review of 56 studies showed that the median OS in patients undergoing MX ranged from 36 to 142 months compared to patients not undergoing MX, in whom it ranged from 8 to 27 months [110]. Performing MX was associated with a significant (more than 2-fold) reduction in the risk of death (HR 2.37; 95% CI 2.03–2.87). The most important prognostic factor was the radical resection of the metastases. Other favorable prognostic factors were: ECOG performance status 0-1, clear cell histology, ISUP grade 1–2, time from nephrectomy to relapse > 12 months, presence of metastases in the lungs, pancreas, liver, thyroid gland and adrenal glands. Patients with metastases limited to the lungs had the best prognosis [110]. Radical MX of lung metastases compared to non-radical management is associated with a significant prognosis improvement with median OS of 69 months (radical MX) *versus* 19 months (non-radical MX; P < 0.00001) and a 5-year CSS of 73,6% versus 19%, respectively [111]. Slightly worse results of surgical MX were obtained in cases of metastases of unusual or rare location (skin, muscles, salivary glands, breast, nasopharynx, stomach). In daily practice, it is difficult to define individual indications for surgical treatment of metastases. However, it can be assumed that before implementing systemic therapy, the patient should be carefully assessed in terms of the feasibility and benefits of MX.

Recommendations

— Active surveillance and deferring of systemic treatment may be considered in RCC patients with IMDC risk factor ≤ 1 and metastases in ≤ 2 organs (II, B).
— Cytoreductive nephrectomy should be considered in RCC patients with synchronous metastases and IMDC risk factor ≤ 1 (I, B).
— In RCC patients with synchronous metastases and IMDC risk factors ≥ 2 cytoreductive nephrectomy is contraindicated (I, B).
— Surgical metastasectomy or radiosurgery should be considered in RCC patients with oligometastatic dissemination (II, C).

7.3.4. Adjuvant systemic therapy

The appropriateness of adjuvant systemic therapy after radical surgery in RCC patients has been assessed in numerous phase III studies. The phase III PROTECT study enrolled patients after radical surgery due to pT2, high-grade renal cell carcinoma or stage ≥ pT3 or pN1 RCC. Patients were randomly assigned to receive either pazopanib or placebo for one year. In the primary endpoint analysis, no significant effect of pazopanib on the time to disease progression was demonstrated [112]. The ASSURE study evaluated the effect of sorafenib or sunitinib treatment on DFS versus placebo. The study included patients without distant metastases, after radical surgery in the pT1b G3–4 N0 stage (patients with N0 feature were allowed to participate based on imaging tests) and with higher local advancement with any grade and patients after radical surgery with metastatic lymph nodes. There were no significant differences in DFS [113]. The only positive study on adjuvant ccRCC treatment remains the phase III S-TRAC study, in which patients received sunitinib or placebo for one year. The study included 615 patients with pT3 tumor or lymph

node involvement after radical surgery. The median DFS was 6.8 years in the sunitinib group and 5.6 years in the placebo group, which translated into a significant reduction in the relative risk of disease recurrence or death by 24% (HR = 0.76; P = 0.03) [114]. In the summary of studies on the effectiveness of TKIs in adjuvant treatment, attention should be paid to the different inclusion criteria in individual studies. However, these differences and distinctness in imaging evaluation methodology make it difficult to fully explain the conflicting results of the ASSURE and S-TRAC studies. Due to these doubts, the European Medicines Agency, in relation to the significant toxicity of TKIs treatment, did not register any drug from this group for the adjuvant treatment of ccRCC.

7.3.5. First-line treatment for patients with clear cell RCC

7.3.5.1. VEGFR tyrosine kinase inhibitors

In patients with metastatic RCC, there are many systemic treatments with proven effectiveness. The evaluation of the studies is made difficult by the inconsistent application of prognostic criteria (earlier — MSKCC criteria, later — IMDC criteria) — both scales distinguish three prognostic groups, but due to slightly different criteria there are some differences in the characteristics of patients in individual studies. Moreover, the inclusion criteria differed in terms of histological type. Only the study on the efficacy of temsirolimus included the patients with neoplasms other than clear cell carcinoma; other studies required to indicate clear cell histology, but the volume of this component in relation to the whole tumor was different in individual studies. Additionally, in some studies, primary tumor resection was required, while in others only confirmation the histological diagnosis was sufficient. In view of the discussion on the role of nephrectomy in metastatic RCC, these differences make it difficult to compare the results of individual studies. Moreover, allowing the patients from comparative group to switch after disease progression to the group receiving an experimental drug (crossover) significantly complicates the inference regarding the impact of the new treatment on OS.

In older studies on the effectiveness of systemic treatment, the comparator was IFN-α — the first drug with proven effectiveness in the treatment of patients with metastatic RCC, but currently of historical importance. In current first-line studies, the comparator is usually sunitinib, the first drug to be more effective than IFN-α.

The Phase III AVOREN study compared the combination of bevacizumab and IFN-α with INF-α monotherapy in metastatic ccRCC. The median PFS increased from 5.4 months for IFN-α to 10.2 months for the bevacizumab plus IFN-α combination. The median OS in this study did not differ significantly for both groups of patients, however, in the AVOREN study, bevacizumab + IFN-α was allowed after progression to IFN-α [115].

Monotherapy with sunitinib in the first-line treatment of advanced RCC was compared with IFN-α in the phase III study, which enrolled patients after surgical treatment of a primary tumor with dominant clear cell histology from favorable and intermediate prognostic group according to the MSKCC scale. Overall survival was longer in patients treated with sunitinib (26.4 months) compared to those receiving IFN-α (21.8 months) despite sunitinib treatment in patients with progression in the group primary treated with IFN-α. The median PFS was 11 months for sunitinib compared with 5 months for IFN-α, which was also statistically significant. The objective response rates were 47% for sunitinib and 12% for IFN-α. All observed differences were statistically significant [116]. The results of this study ultimately resulted in the ccRCC treatment with IFN-α monotherapy being no longer recommended, and sunitinib becoming the first TKI used in first-line treatment. Another TKI used in the first-line treatment was pazopanib. This drug was compared with sunitinib in the non-inferiority phase III COMPARTZ study. This study demonstrated that pazopanib is not significantly inferior to sunitinib in terms of PFS and OS. The authors of the study raised the issue of better tolerance of pazopanib treatment [117], which to some extent was confirmed in the PISCES study, comparing patients' treatment preferences. Patients preferred pazopanib (70% *vs.* 22%) because of less symptomatic toxicity associated with this drug [118]. Pazopanib is approved in Europe for the first-line treatment of adult patients with advanced RCC and for the treatment of patients who have previously received cytokines for advanced RCC.

Tivozanib was compared with sorafenib in a phase III study in patients with advanced ccRCC. The comparator used — sorafenib — raises doubts because no phase III study has shown its superiority to IFN-α in first-line treatment in terms of efficacy. Although the median PFS after first-line treatment was significantly better for tivozanib than for sorafenib (12.7 months *vs*. 9.1 months), no significant differences in OS were observed [119]. It was surprising that the median OS was higher for sorafenib (29.3 months) than for tivozanib (28.8 months). Tivozanib is approved for the first-line treatment of patients with advanced RCC, but in Poland, this drug is not reimbursed.

In a phase III study comparing axitinib with sorafenib in first-line treatment in metastatic clear cell RCC, no significant difference in the median PFS between the treatment groups was shown — as a result, axitinib was not registered in this indication [120].

In the phase II CABOSUN study, which included 157 patients with advanced RCC with intermediate and high risk according to IMDC, cabozantinib and sunitinib were compared in first-line treatment. Cabozantinib increased median PFS by 3.2 months (8.6 *vs.* 5.3 months, respectively), which translated into a significant reduction in the relative risk of disease progression or death by 52% (HR = 0.48; 95% CI 0.31–0.74). The objective response and clinical benefit rates were 20% and 74%, respectively, for cabozantinib, compared to 9% and 47%, respectively, for sunitinib. Early disease progression occurred in 18% of patients treated with cabozantinib compared to 29% of patients treated with sunitinib. However, the CABOSUN study did not show an improvement in OS with cabozantinib versus sunitinib. Grade 3 or 4 adverse events rates were comparable for cabozantinib and sunitinib. Due to the limitations of the statistical analyzes in phase II study, the evidence is of lower quality and a benefit was only shown for PFS and objective responses [121].

7.3.5.2. mTOR kinase inhibitor

Temsirolimus — mammalian target of rapamycin (mTOR) serine-threonine kinase inhibitor was evaluated in a phase III study in patients with advanced RCC (also with histology other than ccRCC) with an unfavorable prognosis according to the MSKCC scale. Patients were randomized to three treatment arms: (i) temsirolimus monotherapy, (ii) IFN-α monotherapy, or (iii) temsirolimus plus IFN-α combination. Patients receiving temsirolimus achieved significantly better median OS and PFS than patients in the other arms. Median PFS and OS were 5.5 months, 4.7 months, and 3.1 months, and 10.9 months, 8.4 months, and 7.3 months for temsirolimus, IFN-α, and temsirolimus with IFN-α, respectively [122]. Based on this study, temsirolimus has been approved for first-line treatment in patients with advanced RCC with at least 3 risk factors according to MSKCC.

7.3.5.3. Checkpoint inhibitors

In the CheckMate 214 study, two-drug immunotherapy with immune checkpoint inhibitors (ICI): programmed death receptor 1 (PD-1) (nivolumab) and cytotoxic T cell antigen 4 (CTLA-4) (ipilimumab) was compared with sunitinib in patients with metastatic RCC containing a clear cell component. The study showed that immunotherapy is significantly more effective in patients with intermediate and unfavorable prognosis according to the IMDC scale (77% of participants in the study), and the subgroup analysis confirmed these results for both intermediate and unfavorable prognosis [123]. For patients with intermediate and unfavorable prognosis (considered together), median PFS was similar and accounted for 8.2 months (immunotherapy) and 8.4 months (sunitinib), but the use of immunotherapy resulted in a significant reduction of the risk of progression by 23% (HR = 0.77, 95% CI 0.65–0.90). In the unfavorable and intermediate prognostic population according to IMDC, the objective response rates were 42% and 27%, and the complete response rates were 9% and 1% for immunotherapy and sunitinib, respectively. The median OS in the immunotherapy arm was not reached, and in the sunitinib arm was 26.6 months, which translated into a significant reduction in the risk of death in patients with intermediate and poor prognosis by 34% (HR = 0.66; 95% CI 0.54–0.80). The quality of life in patients undergoing immunotherapy was significantly better than that in patients receiving sunitinib. The improvement in prognosis after immunotherapy was independent of programmed death-ligand 1 (PD-L1) expression [124]. The delay in registration of this treatment by the European Medicinal Agency was due to the unclear role of ipilimumab in combination with a PD-1 inhibitor and, according to the recommendation, a study is currently conducted that directly compares the value of nivolumab with or without ipilimumab. Ultimately, based on the study, nivolumab in combination with ipilimumab has been approved in Europe for the first-line treatment of advanced RCC in adult patients with intermediate or poor prognosis.

7.3.5.4. Checkpoint inhibitors in combination with kinase inhibitors

In the phase III Keynote-426 study, the combination of axitinib and pembrolizumab with sunitinib monotherapy was compared in the first-line treatment of patients with advanced ccRCC. The study showed that the estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab/axitinib arm and 78.3% in the sunitinib arm. The corresponding estimates for the 18-month OS rate were 82.3% and 72.1%, respectively. Median OS was not reached in either group. The combination of pembrolizumab and axitinib was associated with a significant reduction in the relative risk of death by 47% compared with sunitinib (HR = 0.53; 95% CI 0.38–0.74). Median PFS was 15.1 months in the experimental group and 11.1 months in the sunitinib group, which translated into a significant reduction in the relative risk of disease progression by 31% (HR = 0.69; 95% CI 0.57–0.84). The benefits of pembrolizumab and axitinib in relation to OS and PFS were observed in all IMDC risk categories (however, only in the intermediate and unfavorable groups these differences were statistically significant), regardless of PD-L1 expression [125]. Based on this study, pembrolizumab in combination with axitinib has been approved for the first-line treatment of patients with advanced ccRCC.

In another phase III study, the effectiveness of axitinib in combination with avelumab in patients with metastatic RCC with a clear cell component was

compared with sunitinib in the first-line treatment. The median PFS was 13.8 months in the avelumab plus axitinib arm compared with 8.4 months in the sunitinib arm (hazard ratio of progression or death 0.69). Among patients in the overall population with high, intermediate and low risk according to IMDC who received avelumab with axitinib, 68.1%, 51.3%, and 30.6%, respectively, achieved objective responses compared with 37.5%, 25.4 % and 11.3% of patients who received sunitinib. There are no data on OS in this study [126]. In Europe, avelumab is approved in combination with axitinib for the first-line treatment of adult patients with advanced RCC.

Recommendations

— In patients after radical surgery due to renal cell carcinoma, systemic adjuvant therapy is not recommended (I, A).
— Treatment with bevacizumab in combination with interferon-α does not improve overall survival compared to interferon- α alone and is not the treatment of choice (I, C).
— Sunitinib and pazopanib are drugs of comparable activity in advanced renal cell carcinoma patients with favorable and intermediate prognosis (I, A).
— Sunitinib and pazopanib have proven value, but in some patients, immunotherapy or immunotherapy in combination with kinase inhibitors should be considered first (I, B).
— Axitinib monotherapy should not be used in the first-line treatment of patients with advanced renal cell carcinoma (I, A).
— Cabozantinib is more active than sunitinib in the treatment of RCC patients in intermediate and unfavorable prognosis in terms of progression-free survival, but an effect on overall survival has not been proven (I, B).
— The use of cabozantinib should be considered in patients with clear cell renal cell carcinoma, intermediate and poor prognosis, and with contraindications to checkpoint inhibitor-based therapies, especially if a rapid response is required (I, B).
— Temsirolimus improves the prognosis of RCC patients in poor prognosis group but compared to other treatments the clinical benefit is very limited (I, C).
— The use of the combination of nivolumab and ipilimumab in patients with renal cell carcinoma in intermediate and poor prognosis groups significantly improves the prognosis in terms of progression-free and overall survival compared to sunitinib (I, A).
— The combination of pembrolizumab with axitinib in relation to sunitinib in patients with RCC significantly improves the prognosis in terms of progression-free and overall survival, while being associated with a very low risk of lack of benefit from the treatment (I, A).

7.3.6. Second-line treatment for patients with clear cell RCC

Historically, second-line treatment has only been considered in patients with advanced ccRCC after the failure of cytokines (e.g. IFN-α). Drugs with significant activity compared to placebo on PFS — but not OS — were sorafenib, pazopanib and axitinib. It should be remembered that cytokines, which are no longer used in practice in RCC patients, have a completely different mechanism of action than ICI. Therefore, the extrapolation of data regarding TKIs activity after cytokines to their usefulness after ICIs is unjustified.

7.3.6.1. Treatment after tyrosine kinase inhibitors

The first drug with proven activity in patients after failure of TKI treatment was everolimus, which is an mTOR kinase inhibitor. In the phase III RECORD-1 study, in patients who failed therapy with sunitinib and/or sorafenib, everolimus significantly increased the median PFS by 3 months (4.9 months versus 1.9 months) compared with placebo, reducing the relative risk of progression by 67% (HR = 0.33; P < 0.001) [127]. In this study, however, no significant benefit of everolimus treatment was observed in relation to OS (the study assumed the administration of active drug after progression on placebo). Although the drug was associated with side effects, no significant differences in terms of patients' quality of life were found. Axitinib was the first TKI with marked second-line treatment activity following the failure of TKI therapy. In the phase III study, axitinib significantly increased median PFS from 5.7 months to 8.3 months compared to sorafenib, which translated into a 35% reduction in the relative risk of progression (HR = 0.65; P < 0.0001). However, no significant differences were observed with regard to OS (median 19.2 months and 20.1 months, respectively) [128].

Significant progress in the treatment of second-line RCC patients occurred with the advent of nivolumab and cabozantinib. In parallel clinical trials, both drugs for the first time in history significantly increased OS in patients with ccRCC after failure of TKI therapy compared to the active comparator, everolimus [129, 130]. In the Check-Mate 025 study, the use of nivolumab versus everolimus resulted in a significant reduction the risk of death by 27% (HR = 0.73; 95% CI 0.62–0.85) with no significant effect on PFS (HR = 0.88; P = 0.11). Nivolumab also provides a clinical benefit in 60% of patients with an objective response rate of 26%, however, in over one-third of patients (35%) no benefit was observed from the use of nivolumab (disease progression at the first assessment) [130]. Nivolumab caused typical side effects related to the activation of autoimmune mechanisms, but the quality of life of patients was better compared to patients taking everolimus [131].

In turn, the use of cabozantinib in the METEOR study compared to everolimus was associated with a significant reduction the risk of both death — by 30% (HR = 0.70; 95% CI 0.58–0.85) and progression — by 42% (HR = 0.58; 95% CI 0.45–0.75) [129]. Cabozantinib led to clinical benefit in 87% of patients with an objective response rate of 24%, and only less than 10% of patients did not benefit from the treatment. Clinically significant side effects of cabozantinib were mainly diarrheas, which were more frequent and severe than for other TKIs. On the other hand, the profile of other side effects can be considered typical for this drug class. Despite the higher incidence of adverse events in the arm receiving cabozantinib, the quality of life of patients treated with this drug did not differ significantly in relation to everolimus. Additionally, the time to significant deterioration in the quality of life of patients was significantly longer for cabozantinib [132].

Currently, nivolumab and cabozantinib are the drugs of choice for the second-line treatment of patients with advanced ccRCC. Both drugs significantly improve the prognosis, and the drug should be selected carefully with regard to potential benefits and risks. The subgroup analyzes in the study with nivolumab found that the drug is active in intermediate and poor prognosis group according to IMDC scale. As nivolumab did not show a significant effect on PFS, and more than 30% of patients will not benefit from its use, it is the optimal choice in patients without cachexia, asymptomatic or poorly symptomatic, without the risk of organ crisis, and not receiving antibiotic therapy within the preceding month. On the other hand, cabozantinib seems to be a better option for second-line treatment in patients with favorable and intermediate prognosis according to IMDC scale, with cancer-related symptoms and advanced disease, and requiring a quick and profound response to treatment.

7.3.6.2. Treatment after immunotherapy with nivolumab and ipilimumab

Due to the lack of prospective clinical trials assessing the effectiveness of systemic treatment of patients receiving modern immunotherapy based on the combination of ipilimumab and nivolumab, the use of cabozantinib seems to be the optimal management. Retrospective analyzes of the METEOR study showed that cabozantinib was more active than everolimus in patients receiving prior-line immunotherapy based on ICI.

7.3.6.3. Treatment after immunotherapy combined with a tyrosine kinase inhibitor

There is currently no evidence of the effectiveness of any systemic therapy in RCC patients after failure of ICI and TKI containing therapy (e.g. pembrolizumab and axitinib). Therefore, the procedure of choice is to enroll patients previously receiving such treatment for clinical trials. If impossible, the use of other TKIs (especially cabozantinib, if not used as part of combination therapy) or everolimus could be considered.

Recommendations

— Cabozantinib and nivolumab are the drugs of choice in the second-line treatment of patients with clear cell renal cell carcinoma (I, A).
— Patients who received a multi-kinase inhibitor (sunitinib, pazopanib) in the first line should receive cabozantinib (I, A) or nivolumab in the second line (I, A).
— Patients who received nivolumab with ipilimumab in the first line should receive cabozantinib (III, B) or axitinib in the second line (IV, B).
— In patients who received a combination of immunotherapy and a tyrosine kinase inhibitor in the first line, the use of another TKI (if not used as part of combination therapy) or everolimus may be considered in the second line (IV, C).
— The use of cabozantinib in the second-line treatment is associated with the lowest risk of treatment failure (I, C).

7.3.7. Third-line treatment for patients with clear cell RCC

Third-line treatment should be considered in patients in good performance status and with preserved organ capacity, with no contraindications to systemic treatment. This procedure prolongs the OS [133, 134]. The benefits of fourth and subsequent lines of treatment are limited [135–137] and should only be considered in selected patients. The choice of the appropriate therapeutic strategy depends on the clinical situation and the type and tolerability of previous treatment. Including patients in clinical trials is preferable option.

7.3.7.1. Molecularly targeted drugs

In the phase III study, which compared the efficacy of cabozantinib and everolimus after failure of anti-angiogenic treatment, 29% of patients had previously received two or more treatment lines (including ICI in nearly 5%). In this group, the efficacy of cabozantinib was significantly higher — the reduction in the relative risk of progression was 49% (HR 0.51; 0.35–0.74) [129]. Cabozantinib activity in the third and subsequent lines of treatment, including after previous ICI use, has also been demonstrated in retrospective studies [138, 139]. On the other hand, the GOLD study confirmed the activity of sorafenib in the third-line treatment in the population of patients previously treated with TKI-VEGFR and everolimus. The use of sorafenib was associated with a reduction in tumor mass in 46% of patients, and objective response was observed in 4% of patients [140].

In the population included in the aforementioned RECORD-1 study, 26% of patients had previously received two lines of TKI-VEGFR treatment (sunitinib and sorafenib) [127]. Everolimus was associated with an increase in PFS compared to placebo (median 4 months and 1.8 months, respectively). However, considering the lower activity of everolimus in relation to cabozantinib and nivolumab, it seems rational to use it in patients after failure of sequential therapy with the use of the above-mentioned drugs or when the above-mentioned drugs cannot be used.

7.3.7.2. Immunotherapy

Currently, nivolumab is the only ICI approved for the treatment of patients with advanced RCC after failure of prior therapy. In the already mentioned pivotal study, Check-Mate 025, 28% of patients received nivolumab in third-line treatment [130]. The relative risk of death in this group decreased by 11% (HR 0.89; 95% CI 0.61–1.29), while a post-hoc analysis showed a reduction in the risk of death by 35% (HR 0,65; 95% CI 0.43–0.99) [141].

In fourth or subsequent treatment line, the decision regarding treatment strategy should be made on an individual basis, taking into account prior management, response to treatment, and tolerability (including persistent complications of prior treatment). It is acceptable to use everolimus, TKI-VEGFR other than previously used or re-use of TKI-VEGFR, if such treatment was effective in the past. Re-use of immunotherapy is not recommended.

Recommendations

— Third-line treatment should be considered in patients with metastatic renal cell carcinoma in good performance status, with no contraindications to systemic therapy (III, A).
— The decision to use the fourth or subsequent treatment lines should be made on an individual basis (IV, C).
— Patients with metastatic renal cell carcinoma after sequential use of multi-kinase inhibitors should receive nivolumab in third-line treatment (I, B).
— Patients with metastatic renal cell carcinoma after sequential treatment with a tyrosine kinase inhibitor and nivolumab should receive cabozantinib in third-line treatment (I, B).
— In patients with metastatic renal cell carcinoma, sorafenib (I, B), cabozantinib (IV, B) or nivolumab may be used in third-line treatment after treatment with a multi-kinase inhibitor and everolimus.
— Patients with metastatic renal cell carcinoma after sequential treatment with ipilimumab plus nivolumab, followed by a multi-kinase inhibitor, should receive cabozantinib in third-line treatment (IV, B).
— Patients with metastatic renal cell carcinoma after sequential treatment with ipilimumab plus nivolumab followed by cabozantinib should receive everolimus in third-line treatment (IV, C).
— Patients with metastatic clear cell renal cell carcinoma after sequential treatment with a multi-kinase inhibitor combined with immunotherapy followed by cabozantinib should receive everolimus in third-line treatment (IV, C).

7.3.8. Treatment for patients with advanced non-clear cell RCC

Data on the effectiveness of systemic treatment of advanced RCCs other than clear cell histology (non-ccRCC) are limited. Due to their relatively rare occurrence, their representation in the populations of patients included in prospective phase III clinical trials was small or the protocols completely excluded the possibility of their recruitment. For this reason, in non-ccRCC cases, it is advisable to qualify patients for controlled clinical trials. Current knowledge about the efficacy of available therapeutic options in the treatment of non-ccRCC is based primarily on the results of small prospective studies or subgroup analyzes in larger studies that generally assessed the effectiveness of TKI or serine-threonine kinase inhibitors [142, 143].

The greatest amount of data in the non-ccRCC patient population relates to the use of sunitinib. Due to the design of these studies and their statistical assumptions, the obtained results could not provide unambiguous answers regarding the efficacy of the tested drugs in patients with non-ccRCC; a trend suggesting the advantage of sunitinib over everolimus was observed. These data were confirmed in further expanded access studies, subsequent retrospective analyzes, and subgroup analysis in the registration process for temsirolimus.

The available data also suggest the effectiveness of other molecularly targeted drugs (everolimus, sorafenib, pazopanib, and temsirolimus), with most studies including only patients with papillary or chromophobe RCC. Recently published results of prospective clinical trials using ICI suggests the clinical activity of this form of immunotherapy in patients with non-ccRCC previously receiving another form of treatment.

Figure 3 presented the algorithm of first-line systemic treatment developed on the basis of the above-mentioned studies and compliant with the ESMO recommendations.

Currently, there are no data based on which the recommendations regarding second-line systemic treatment of patients with non-ccRCC could be developed. Nevertheless, for the most common papillary RCC, the use of drugs as for ccRCC is acceptable.

cMET inhibitors have shown activity in papillary tumors with a confirmed mutation or amplification

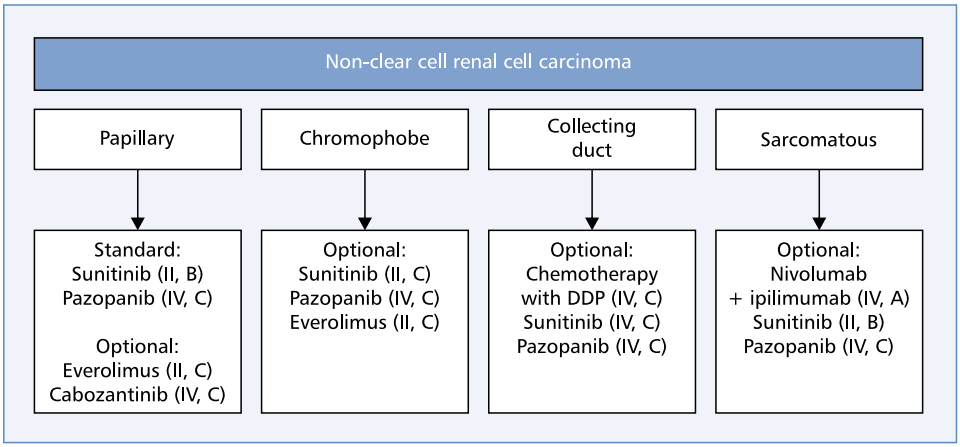

Figure 3. Management of patients with advanced non-clear cell renal cell carcinoma

in the *cMET* gene [144]. In turn, crizotinib and other cMET inhibitors may be an important alternative to classic TKIs with anti-angiogenic activity (anti-VEGF).

Some patients with chromophobe RCC may benefit from treatment with mTOR inhibitors, as it has been shown that mutations in chromosome 7 lead to loss of the functional folliculin gene and, secondly, to increased activity of the mTOR complex.

The available data suggest the presence of excessive inflammatory infiltration within tumors with sarcomatous component, being a histological feature associated with poor prognosis. Renal cell carcinomas with a sarcomatous component appear susceptible to ICI therapy. In this situation, therapeutic strategies such as the combination of nivolumab with ipilimumab or pembrolizumab with axitinib should be considered as an option of choice [124, 125].

Due to the fact that the biology of RCC originating from collective ducts and medullary renal cell carcinomas is very similar to the biology of aggressive forms of cancers originating from transitional epithelial cells, classical chemotherapy is used in patients with these tumor types (e.g. MVAC regimen with cisplatin gemcitabine) [145–147]. Unfortunately, treatment outcomes for these RCC subtypes remain unsatisfactory, with objective response rates below 30%. There is also no direct comparison of the individual regimens in these indications [148, 149]. However, scant data on the effectiveness of immunotherapy in this group of patients suggest a negligible clinical benefit of the available therapeutic options [148].

7.3.9. Anti-osteolytic drugs

The use of zoledronic acid in RCC patients with multiple bone metastases is a palliative approach that reduces the incidence of skeletal complications and prolongs the time their onset without significant affecting OS. Renal function monitoring is essential when taking zoledronic acid. Administration of zoledronic acid may be considered in patients with metastatic RCC with longer survival expected. A comparable value was demonstrated for denosumab.

7.4. Radiotherapy

Renal cell carcinoma is considered to be radioresistant and radiotherapy is not a routinely recommended treatment.

Preoperative radiotherapy

The results of the only prospective studies of the use of preoperative radiotherapy in the treatment of primary operable RCC were published in the 1970s. In both of them, low total doses of radiation were administered: 30 Gy in 15 fractions of 2 Gy each or 33 Gy in 15 fractions of 2.2 Gy each using standard radiotherapy techniques. There has been no evidence of improvement in 5-year survival compared to standalone nephrectomy [150]. Currently, such a strategy is not recommended.

Intraoperative radiotherapy

There are only single reports of intraoperative radiotherapy in RCC patients, mainly locally advanced or with local tumor recurrence. A study involving the largest group of 98 patients showed results comparable to standalone nephrectomy in cancer-related and asymptomatic survival [151]. Due to the scarcity of data, intraoperative radiotherapy is not recommended and should only be used in clinical trials.

Postoperative radiotherapy

The role of radiotherapy in the adjuvant treatment of patients with locally not advanced RCC after nephrectomy has not been clearly established. The experiences from the 1970s and 1980s showed that the treatment results deteriorated after adjuvant radiotherapy [152].

However, studies from that period are vitiated by methodological errors (e.g. small groups of incorrectly selected patients) and used radiotherapy techniques that did not allow for effective dose reduction in critical organs — this was a likely cause of higher toxicity of treatment and a lower 5-year survival rate in patients undergoing radiotherapy compared to the group undergoing surgery alone. Later studies also failed to confirm the value of adjuvant radiotherapy [153]. A meta-analysis of data from seven studies (two prospective and five retrospectives) showed an increase in local cure rates after postoperative radiotherapy but with no effect on OS [154]. Coming to conclusion, postoperative radiotherapy may be considered in patients with a high risk of local recurrence, mainly with positive surgical margins and metastases to regional lymph nodes. However, it should only be used in clinical trials until its value is confirmed in randomized trials using modern radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT).

Standalone radiotherapy

The opinion about RCC radioresistance may be wrong because the use of modern radiotherapy techniques allows the administration of high radiation doses in one (stereotactic radiosurgery, SRS) or several fractions (stereotactic body radiotherapy, SBRT). Therefore, it allows also to overcome radioresistance while reducing the risk of damage to healthy tissues. This procedure, apart from direct destruction of cancer cells by activation of the ceramide signaling pathway, may also induce the so-called abscopal effect. Released products of tumor cell lysis become visible to the immune system, causing its "unmasking" and effective destruction of cancer cells. This effect can be enhanced by the simultaneous use of molecularly targeted therapies. The experience regarding stereotactic radiotherapy of RCC brain metastases, showing local control improvement, has become the basis for using this method in patients with locally advanced RCC who are not eligible for nephrectomy [155]. Several prospective studies have shown promising 2-year local cure rates of over 90% with acceptable toxicity. The lack of evidence from randomized trials does not allow to determine neither the optimal dose of radiation nor the method of fractionation or to recommend such a treatment in routine clinical practice. Primary RCC radiosurgery and stereotactic radiotherapy should only be used in clinical trials.

Radiotherapy in oligometastatic disease

Many retrospective studies show improved treatment outcomes in patients with RCC after primary nephrectomy who underwent metastasectomy, radiosurgery, or stereotactic radiotherapy after oligometastatic disease recurrence [156, 157]. For both intracranial and extracranial metastases, local control rates account for up to 90%, and the median OS is 7 to 26 months. In prospective randomized studies, the effect of tumor bed postoperative radiosurgery on the reduction of local recurrence risk in patients with brain metastases after complete metastasectomy compared to observation was confirmed. Additionally, it has been shown reduced cognitive impairment compared with total brain irradiation [158, 159].

Radiosurgery and stereotactic radiotherapy are recommended treatment methods in patients with RCC brain metastases.

Achieving control of metastatic lesions in the brain with radiotherapy is indicated before starting anti-angiogenic treatment.

Palliative radiotherapy

Numerous reports indicate that radiotherapy is an effective method of controlling symptoms related to local progression or dissemination of RCC. It enables the reduction of pain caused by spreading to the bone or infiltration of nerve plexuses and managing the symptoms associated with multiple metastases in the brain. The administered total doses and applied fractionation methods depend mainly on patient's performance status, location of metastases and the volume of irradiated tissues. Response to radiotherapy is achieved in more than 50% of patients [160, 161]. Radiotherapy is the method recommended for symptom control in patients with metastatic RCC.

Recommendations

— Stereotactic radiotherapy is the recommended treatment option in patients with renal cell carcinoma with metastases to the central nervous system (II, A).
— Radiotherapy is a valuable therapeutic option in the symptomatic treatment of patients with metastatic renal cell carcinoma (III, B).
— Stereotactic radiotherapy is an alternative to surgical metastasectomy (III, B).

8. Follow-up after treatment completion

The objectives of observation of RCC patients after the completion of surgical treatment include monitoring and/or diagnosing the nature of postoperative complications and dysfunction, as well as the detection of local recurrences or contralateral RCC and distant metastases.

There is no consensus on the post-treatment monitoring principles in RCC patients. There are also no prospective studies analyzing the prognosis of patients depending on the time of relapse diagnosis. Intensive surveillance with the use of imaging tests is not necessary

in all patients, but follow-up after treatment completion is warranted (especially in patients receiving treatment with radical intent). Large long-term cohort observational studies are available [162, 163]. They demonstrated a benefit in terms of survival in patients undergoing a structured observation protocol compared to unobserved patients [164]. The long-term results after surgery for low-stage tumors (T1a) are almost always excellent. Therefore, a gradation in the intensity of monitoring based on the risk of relapse and/or disease generalization is warranted. The risk should be determined based on the UCLA Integrated Staging System (UISS) for Renal Cell Carcinoma [165, 166] (Table 9). Therefore, personalized and risk-based monitoring after treatment completion with regular imaging examinations is currently recommended (Table 10).

CT is most commonly used for oncological monitoring, and ultrasound is used only in some cases. PET-CT, PET-MR and scintigraphy are not routinely recommended. In low-risk patients, follow-up should take into account the expected benefits and exposure to ionizing radiation. MR imaging can be used to reduce

Table 9. UCLA Integrated Staging System (UISS) for renal cell carcinoma

Localized disease (any T, N0, M0)			
Primary tumor (T)	**Differentiation**	**ECOG performance status**	**Risk**
T1	Fuhrman 1–2	0	Low
		≥ 1	Intermediate
	Fuhrman 3–4	Any	
T2	Any	Any	
T3	Fuhrman 1	0	
		≥ 1	
	Fuhrman > 1	0	
		≥ 1	High
Metastases (N1, N2 or M1)			
N1M0	Any	Any	Low
N2M0/M1	Fuhrman 1	0	
		≥ 1	Intermediate
	Fuhrman 2	0	Low
		≥ 1	Intermediate
	Fuhrman 3	Any	
	Fuhrman 4	0	
		≥ 1	High
Prognosis			
Stage	**Risk**	**5-year survival rate**	
Localized disease	Low	91.1%	
	Intermediate	80.4%	
	High	54.7%	
Metastatic disease	Low	32%	
	Intermediate	19.5%	
	High	0%	

Table 10. Schedule of follow-up of RCC patients after completion of surgical treatment

Risk profile	**Observation**				
6 months	**1 year**	**2 years**	**3 years**	**> 3 years**	
Low	US	CT	US	CT	CT every 2 years, patient education about the risk of recurrence accounting for app. 10%
Intermediate/high	CT	CT	CT	CT	CT every 2 years

CT — computed tomography of chest and abdomen, alternatively abdominal imaging with the use of magnetic resonance imaging; US — ultrasound of abdominal cavity, kidney/kidneys and/or postoperative tumor bed

radiation exposure. Chest, abdominal and pelvic CT scans should be performed in patients from moderate or high-risk groups.

Post-treatment follow-up should also include monitoring of renal function, including the measurement of serum creatinine concentration along with GFR. Repeated and long-term monitoring of upper urinary tract functioning is indicated in the presence of renal dysfunction both before and after surgery [167]. Regular evaluation of cardiovascular risk factors is also recommended.

In patients undergoing partial nephrectomy, local disease recurrence is rare, but it is important to recognize it early, due to the potential qualification for radical re-treatment [168, 169]. Relapse of the underlying disease in the second kidney is also rare (1–2%), and it may occur late (median 5–6 years) and may be associated with positive surgical margins, multifocal lesions, and higher histopathological grade [170]. In addition to early detection of local recurrence, proper monitoring of patients with RCC after treatment is also aimed at early detection of distant metastases. In late-diagnosed metastatic disease, local treatment options are usually limited (surgical metastasectomy, stereotactic radiotherapy), which are the treatment of choice in oligometastatic disease. Furthermore, detecting relapse/cancer generalization with a low total tumor mass can increase the effectiveness of systemic therapy.

Controversies concern the optimal duration of observations. According to some authors, continuing imaging tests beyond 5 years is cost-ineffective; however, late metastases occur more often as single lesions, which justifies an aggressive treatment approach with curative intent. In turn, in patients with newly diagnosed tumor in contralateral kidney, the detection of the tumor at an early stage often enables nephron-sparing surgery. For tumors <4 cm, there is no difference between partial and radical nephrectomy in relation to recurrence during follow-up [171]. Currently, various nomograms are available to estimate the likelihood of cancer recurrence, metastasis development, or later death, which can be used in everyday clinical practice [172, 173].

Recommendations

— The strategy for monitoring RCC patients after treatment completion should be based on the relapse risk (III, A).
— Patients should be closely monitored after NSS with a positive surgical margin or if the tumor size exceeds 7 cm (III, C).

Conflict of interest

PW — speaker, scientific advisor, presenter - Roche, Ipsen, Pfizer, Novartis, MSD, BMS, Merck

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